IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Shaughnessy, J.D. et al

FILED: December 04, 2003

SERIAL NO.: 10/727,461

FOR: Identification of Molecular Determinants Of Myeloma Bone Disease

§ ART UNIT: 1642
§
§ EXAMINER:
§ Fetterolf, B. J
§
§ CONFIRMATION NO.
§ 6235
§
§ DOCKET:
§ D6485

MS Non-Fee Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION UNDER 37 C.F.R.§ 1.132

Dear Sir:

I, John D. Shaughnessy, hereby state as follows:

I am an inventor of the above-referenced U.S. patent application Serial No. 10/727,461 and I am aware of the contents of the Office Action, mailed September 14, 2006. In this Office Action, an issue relating to the patentability of the claimed method of diagnosing DKK1-associated lytic bone disease in an individual by measuring expression levels of DKK1 is the degree of enablement provided by the Applicant's specification with regard to the efficacy of the method in diagnosing lytic bone disease, based on measuring DKK1 expression levels, in a variety of disorders such as osteoporosis, post-menopausal osteoporosis and malignancy related bone loss. The following data is presented as evidence of enablement commensurate with the scope of the claims:

The Effects of Neutralizing Antibody against DKK1 on Bone Mineral Density in the Preclinical Nonmyelomatous SCID-rab model

The effects of the neutralizing antibody against DKK1 were determined in nonmyelomatous SCID-rab mouse, constructed by subcutaneous implantation of rabbit bones. The mice received polyclonal anti-DKK1 antibody at a concentration of 50 μg/injection/3 times a week in 4 experiments. In 3 experiments, the experimental mice received monoclonal anti-DKK1 antibody at concentration of 100μg/injection/5 times a week. Experiments were continued for 4-6 weeks. The effects of DKK1 neutralizing antibody on the bone mineral density of implanted femurs in nonmyelomatous mice (n=18), and the uninvolved murine femur of myelomatous SCID-Rab mice (n=9) was determined.

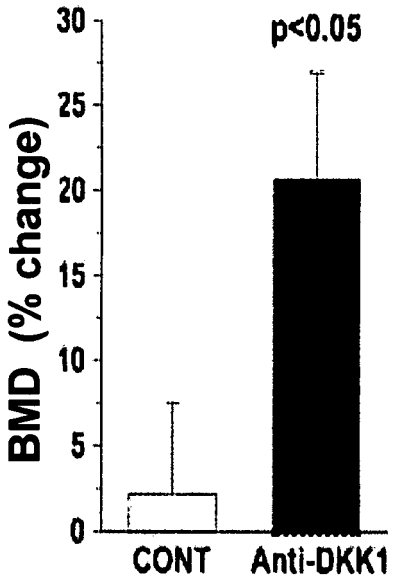
Figures A, B, and C clearly demonstrate that treatment with the DKK1 antibody resulted in a significant increase in bone mineral density of the nonmyelomatous implanted bone relative to controls (treated with irrelevant IgG antibody for 4-6 weeks) (19±6% vs. 3±5%; $p<0.05$) and in the murine femur (4.4±0.6% vs. 0.1±1.4%; $p<0.015$) (Figures A-C). The bone mineral density of uninvolved mouse femurs from myelomatous hosts did not change in both DKK1 AB-treated and controls (4.0±3.2% vs. 3.4±2.5%) (Figures A-C). These data demonstrate that blocking of DKK1 activity results in bone anabolic effects on non-myelomatous bones, further suggesting that DKK1 neutralization may have a broad application in bone disorders. Based on the results of these *in vivo* data, a person having ordinary skill in this art would readily recognize the critical role of DKK1 in

bone remodeling as well as the fact that the claimed methods of the instant invention will be applicable to non-myeloma related bone disorders.

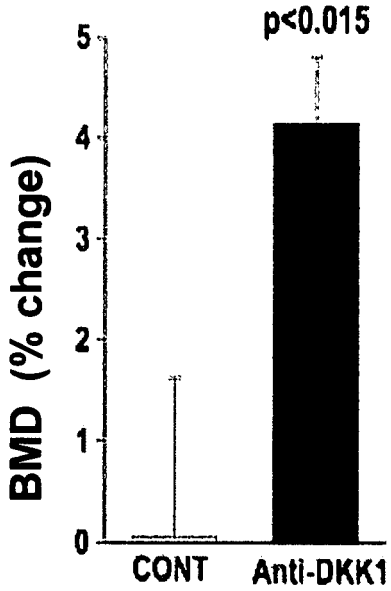
I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 or Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/30/06

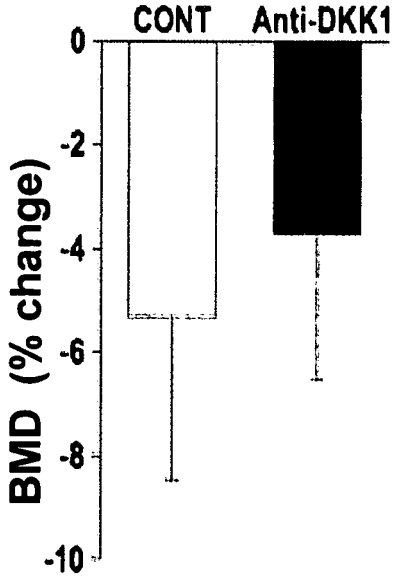
Dr. John D. Shaughnessy



A. Non-Myelematous Implanted Bone



B. Mouse Femur



C. Uninvolved Mouse Femur